BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 16/46, A61K 35/14, 39/395 // C07K 16/28, 14/735

A1

(11) International Publication Number: **WO 96/40788**

(43) International Publication Date: 19 December 1996 (19.12.96)

(21) International Application Number: PCT/US96/09071

(22) International Filing Date: 5 June 1996 (05.06.96)

(30) Priority Data:
08/479,902 7 June 1995 (07.06.95) US

(71) Applicant: MEDAREX, INC. [US/US]; 1545 Route 22 East, Annandale, NJ 08801-0992 (US).

(72) Inventors: GUYRE, Paul, M.; Pinneo Road, Hanover, NH 03755 (US). FANGER, Michael; 54 Blueberry Hill Road, R.R. 1, Box 421, Lebanon, NH 03766 (US).

(74) Agents: ARNOLD, Beth, E. et al.; Lahive & Cockfield, 60 State Street, Boston, MA 02109 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTI-ALLERGY BISPECIFIC MOLECULES

h22 hinge region:

[A]

- ACT CAC ACA TGC CCA CCG TGC CCA — CH2 — CH3
  T H T C P P C P

↓

[B]

BamHI
- ACT CAC ACA TGC CCA CCG TGA GGA TCC -
  T H T C P P •

↓

[C]

XhoI *NotI* *BamHI*
- ACT CAC ACA TGC TCG AGC CTT CAC GGC GGC CGC TGA GGA TCC
  T H T C S S L H G G R •

(57) Abstract

Compositions comprising an anti IgE portion and an anti-effector cell portion, that are useful in preventing an IgE mediated allergic reaction; or that can present an allergen thereby initiating a "vaccine effect" are disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

Anti-Allergy Bispecific Molecules

Background of the Invention

The binding of an allergen to an immunoglobulin E (IgE) receptor on a mast cell initiates the release of histamines and proteases from the cytoplasmic mast cell granules and the synthesis of prostaglandins and leukotrienes that mediate the inflammatory and immediate hypersensitivity responses characteristic of allergies and asthma. Considerable evidence indicates that this response occurs when two or more high-affinity IgE receptors (Fc εR) are crosslinked via IgE molecules that in turn are bound to an allergen molecule (Metzger, H. et al., (1988) *Annu. Rev. Immunol.* 4:419-470).

Many immune system effector cells (e.g., monocytes, macrophages neutrophils, natural killer (NK) cells and dendritic cells), have surface receptors that bind the Fc portion of an immunoglobulin. When such cells encounter target cells that have been opsonized with immunoglobulin antibodies, they form conjugates, and either lyse or phagocytose the target cells, depending upon the effector cell type, the target cell type and the specific Fc receptor type (FcR) involved.

Target cell conjugation with an effector cell and lysis has also been accomplished using bispecific molecules, comprising, for example, an anti-Fc receptor antibody and an antibody directed against a target cell epitope. Complexes of effector cells bound via their Fc receptors to bispecific molecules can specifically bind and lyse target cells which have not been opsonized, but which express the appropriate target antigen.

The binding of a bispecific molecule to an effector cell via an Fc receptor can be susceptible to inhibition by physiological concentrations of immunoglobulin (since immunoglobulins also bind to Fc receptors). However, monoclonal antibodies, which bind to a site on an Fc receptor that is distinct from the binding site for endogenous immunoglobulin, have been produced (see, for example, U.S. Patent 4,954,617; Anderson et al., *J. Biol. Chem.* 261:12856 (1986); and Shen et al., *J. Immunol.* 137:3378-3382 (1986)).

Summary of the Invention

In one aspect, the invention relates to bispecific molecules, which comprise an anti-immunoglobulin E (IgE) portion and an anti-effector cell portion. In a preferred embodiment, the anti-effector cell portion specifically binds an Fc receptor (FcR) on an effector cell. Most preferably the anti-Fc receptor portion of the bispecific molecule binds an FcR at a site, which is distinct from the binding site for the Fc portion of an immunoglobulin.

In another preferred embodiment, the anti-IgE portion is an Fcε receptor (FcεR) or an IgE binding fragment thereof (e.g. an IgE binding portion of an FcεR α- chain). In another aspect, the invention relates to IgE specific effector cells comprising the bispecific molecules complexed to an appropriate effector cell.

In a further aspect, the invention relates to therapeutic and prophylactic uses of the bispecific molecules and IgE specific effector cells based on their ability to bind circulating IgE molecules or allergen bound IgE *in vivo*. For example, the instant claimed bispecific molecules and IgE specific effector cells can prevent IgE binding to mast cells and basophils, thereby preventing an allergic response. In addition, bispecific molecule mediated binding of effector cells to antigen bound IgE can result in effector cell presentation of the antigen, thereby resulting in a vaccine-like effect, by directing the immune system away from production of allergen-specific IgE antibodies towards production of allergen-specific IgG antibodies leading to a permanent "cure" of the allergic response.

The biological activity of the bifunctional molecules and IgE specific effector cells mimic normal physiology. Therefore the compounds should prove to be safe and effective therapeutic agents. The above discussed and many other features and advantages of the present invention will become better understood by reference to the following Detailed Description.

Brief Description of the Figure

The Figure is a diagram showing the nucleotide and amino acid residue sequences of a portion of the hinge region of a humanized Fcγ RI antibody, H22. [A] that was altered to produce a truncated single-sulfhydryl version [B] and then altered further to engineer two unique cloning sites [C]. Underlined nucleotides indicate changes from the previous sequence. Overlined nucleotides are the recognition sequences for the indicated restriction sites.

Detailed Description of the Invention

As used herein, the following terms and phrases shall have the meanings set forth below:

A "bispecific molecule" shall refer to a molecule, which minimally comprises an anti-Fc receptor portion; and an anti-IgE portion. The term bispecific molecule also encompasses molecules which can recognize additional molecules (i.e. are multispecific).

An "anti-effector cell portion" refers to an antibody, a functional antibody fragment (e.g. Fab fragment) or a ligand that recognizes and binds to an effector cell. In a preferred embodiment, the anti-effector cell portion binds to an Fc receptor on an effector cell. Preferred antibodies for use in the subject invention bind the Fc receptor on an effector cell at a site which is not bound by the FcR of an endogenous immunoglobulin. Examples of epitopes to which the anti-effector cell can bind include human FcγR (i.e. FcγRI (CD64), Fcγ RII or FcγRIII), FcαR (CD89), CD33 and P155. Preferred humanized anti-FcγR monoclonal antibodies are described in PCT application WO 94/10332 and U.S. Patent No. 4,954,617, the teachings of which are fully incorporated herein by reference.

An "anti-IgE portion" refers to a ligand that recognizes and binds to IgE alone or IgE bound to an allergen. A preferred anti-IgE portion is an IgE receptor (i.e.FcεR) or an IgE binding fragment thereof (e.g. the FcεR α- chain) or an anti-IgE antibody which may or may not block binding of IgE to an IgE receptor. The nucleotide sequence of the α- chain of FcεR are disclosed, e.g. in Shimizu, A. et al., (1988) *Proc. Natl. Acad. Sci. USA 85*:1907-1911; Kinet, J.-P. et al., (1987) *Biochemistry 26*:4605-4610; International Patent Application WO 89/05352; U.S. Department of Health and Human Services Patent Application No. 07/547,892; and U.S. National Institute of Patent Application No. 07/626,704 (both U.S. patent applications being available from the National Technical Information Service). The teachings of the above references are all fully incorporated herein by reference.

An "effector cell" refers to an immune cell. Preferred effector cells for use in the invention are antigen presenting cells. Specific effector cells express specific Fc receptors and carry out specific immune functions. For example, monocytes, macrophages, neutrophils and dendritic cells, which express FcγRI are involved in both specific killing of target cells and presenting antigens to other components of the immune system. The expression of a particular FcR on an effector cells can be regulated by humoral factors such as cytokines. For example, expression of FcγRI has been found to be up-regulated by interferon gamma (IFN-γ). This enhanced expression increases the cytotoxic activity of FcγRI cells against targets.

An "IgE specific effector cell" refers to an effector cell, as previously defined, linked to a bispecific molecule, as previously defined, so that the effector cell is brought into contact with IgE alone or bound to an allergen.

An "allergen" refers to a substance that can induce an allergic or asthmatic response in a susceptible subject. The list of allergens is enormous and can include pollens, insect venoms, animal dander dust, fungal spores and drugs (e.g. penicillin). Examples of natural, animal and plant allergens include proteins specific to the following genuses: *Canine*

(Canis familiaris); *Dermatophagoides (e.g. Dermatophagoides farinae)*; *Felis (Felis domesticus)*; *Ambrosia (Ambrosia artemiisfolia*; *Lolium* (e.g. *Lolium perenne* or *Lolium multiflorum)*; *Cryptomeria (Cryptomeria japonica)* ; *Alternaria (Alternaria alternata)*; *Alder*; *Alnus (Alnus gultinosa)*; *Betula (Betula verrucosa)*; *Quercus (Quercus alba)*; *Olea (Olea europa)*; *Artemisia (Artemisia vulgaris)*; *Plantago* (e.g. *Plantago lanceolata)*; *Parietaria* (e.g. *Parietaria officinalis* or *Parietaria judaica)*; *Blattella* (e.g. *Blattella germanica)*; *Apis* (e.g. *Apis multiflorum)*; *Cupressus* (e.g. *Cupressus sempervirens, Cupressus arizonica* and *Cupressus macrocarpa)*; *Juniperus* (e.g. *Juniperus sabinoides, Juniperus virginiana, Juniperus communis* and *Juniperus ashei*) *Thuya* (e.g. *Thuya orientalis*); *Chamaecyparis* (e.g. *Chamaecyparis obtusa*); *Periplaneta* (e.g. *Periplaneta americana)*; *Agropyron* (e.g. *Agropyron repens)*; *Secale* (e.g. *Secale cereale)*; *Triticum* (e.g. *Triticum aestivum*); *Dactylis* (e.g. *Dactylis glomerata)*; *Festuca (e.g. Festuca elatior)*; *Poa* (e.g. *Poa pratensis* or *Poa compressa)*; *Avena* (e.g. *Avena sativa)*; *Holcus* (e.g. *Holcus lanatus)*; *Anthoxanthum (e.g. Anthoxanthum odoratum)*; *Arrhenatherum* (e.g. *Arrhenatherum elatius)*; *Agrostis* (e.g. *Agrostis alba)*; *Phleum (e.g. Phleum pratense)*; *Phalaris* (e.g. *Phalaris arundinacea)*; *Paspalum* (e.g. *Paspalum notatum*); *Sorghum* (e.g. *Sorghum halepensis*); and Bromus (e.g. *Bromus inermis).*

The bispecific molecules of the present invention can be prepared by conjugating the anti-Fc R and anti-IgE portions using methods described in the following Example or that are well-known in the art. For example, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) (see e.g., Karpovsky et al. (1984) *J. Exp. Med.* 160:1686; Liu, M.A. et al. (1985) *Proc. Natl. Acad. Sci. USA* 82:8648. Other methods include those described by Paulus (*Behring Inst. Mitt.* (1985) No. 78, 118-132); Brennan et al. (*Science* (1985) 229:81-83), and Gennie et al. (*J. Immunol.* (1987) 139:2367-2375). Preferred conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL.).

Based on their ability to bind circulating IgE molecules or antigen bound IgE *in vivo*, the compounds can be administered to a subject (e.g. human or animal) for any of a number of therapeutic or prophylactic uses. For example, by preventing IgE binding to mast cells and basophils, the instant claimed molecules can thereby prevent an allergic response in a subject. In addition, bispecific molecule mediated binding of effector cells to allergen bound IgE can result in effector cell presentation of the allergen, thereby inducing a vaccine like effect against the particular allergen. In addition, bispecific molecule mediated binding of effector cells to allergen bound IgE can result in effector cell presentation of the antigen,

thereby resulting in a vaccine-like effect, by directing the immune system away from production of allergen-specific IgE antibodies towards production of allergen-specific IgG antibodies leading to a permanent "cure" of the allergic response.

Bispecific molecules of the present invention can be administered freely in a physiologically acceptable solution or can first be coupled to an effector cell, forming an "IgE specific effector cell", prior to being administered to a subject. Bispecific molecules or IgE specific effector cells can be administered *in vivo* as a suspension of cells in a physiologically acceptable solution. The number of cells administered can be in the order of 10^8-10^9, but will vary depending on the therapeutic purpose. In general, the amount will be sufficient to obtain localization of the effector cell at IgE. The term physiologically acceptable solution, as used herein, is intended to include any carrier solution which stabilizes the bispecific molecules of IgE specific effector cells for administration *in vivo* including, for example, saline and aqueous buffer solutions, solvents, antibacterial and antifungal agents, isotonic agents, and the like. Routes of administering bispecific molecules or IgE specific effector cells to a subject can vary and include intravenous, intramuscular, and intraperitoneal administration.

The instant invention is further illustrated by the following Example, which is not intended to limit the invention in any manner.

Example 1 Generation of Functional H22-IgER Fusion Proteins

Materials and Methods

A. Expression vectors and cloning

Expression vectors for the genomic clones of the heavy (pSVgpt) and light (pSVhyg) chains of H22 are as described in International Patent Application Publication Number: WO 94/10332 entitled, *Humanized Antibodies to Fc Receptors for Immunoglobulin G on Human Mononuclear Phagocytes*. For the Fab-ligand fusion construct, it is unnecessary to alter the light chain. For the heavy chain, however, the CH2 and CH3 domains must be removed and replaced with the coding sequences of the ligands. The heavy chain vector contains two *Bam*HI sites, one in the intron between VH and CH1, and the other just downstream of CH3. Using the BamHI restriction sites, DNA encoding the constant domains is replaced by a truncated version encoding only CH1 and most of the hinge. To do this, the polymerase chain reaction (PCR) is utilized to engineer the new C-terminus of the heavy chain fragment with the alterations shown in Figure 1.

The construct shown in Figure 1 [C], consists of a translation termination codon downstream of the cloning restriction sites, *Xho*I and *Not*I, and upstream of a *Bam*HI site which is used to clone the new PCR generated CHI fragment downstream of VH to generate the fusion protein constructs. The cloning sites, which are located downstream of most of the hinge in order to retain flexibility between the Fd and ligand domains, is used to insert DNA encoding EGF or other ligands. Also, the single Cys residue is retained from the previous construct to allow conjugation for the formation of dimeric molecules.

DNA encoding the α chain of IgER is amplified by PCR to have a *Xho*I site on the N-terminus and a *Not*I site on the C-terminus of the coding region, and then inserted in the proper reading frame into the same sites of the newly engineered H22 heavy chain truncated fragment described above. cDNA encoding the α chain of is obtained from the ATCC (#59957).

B. Expression

The murine myeloma NSO (ECACC 85110503) is a non-Ig synthesizing line and can be used for expression of H22-IgER fusion proteins. The final expression vector, a pSVgpt construct with DNA encoding H22 Fd fused in frame to IgER is transfected by electroporation using a BioRad Gene Pulser to NS0 which had been previously transfected with the pSVhyg construct containing DNA encoding H22 light chain. These polypeptides can be expressed by an Ig promoter and Ig enhancer present in the vectors, and secreted by the mAb 22 heavy chain signal peptide located on the N-terminus of the constructs. One or two days after transfection, mycophenolic acid and xanthine can be added to the media to select for cells that took up the DNA. Individual growing colonies can be isolated and subcloned after binding activity is demonstrated by ELISA.

C. Purification

Cells expressing the H22-IgER fusion protein can be subcloned and expanded. The fusion protein-expressing clone can be expanded and grown in spinner cultures and the supernatant clarified and concentrated. Small scale purification can be performed by affinity chromatography on an anti-human kappa chain affinity column (Sterogene; Carlsbad, CA). The purified protein can be analyzed by SDS-PAGE on a 5-15% acrylamide gradient gel under nonreducing conditions.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANTS: Paul M. Guyre and Michael Fanger

(ii) TITLE OF INVENTION: Anti-Allergy Bispecific Molecules

(iii) NUMBER OF SEQUENCES: 3

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: LAHIVE & COCKFIELD
(B) STREET: 60 State Street, Suite 510
(C) CITY: Boston
(D) STATE: Massachusetts
(E) COUNTRY: USA
(F) ZIP: 02109-1875

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/479,902
(B) FILING DATE: 07-JUNE-1995

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Arnold, Beth E.
(B) REGISTRATION NUMBER: 35,430
(C) REFERENCE/DOCKET NUMBER: MXI-044

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (617)227-7400
(B) TELEFAX: (617)227-5941

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..24

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
ACT CAC ACA TGC CCA CCG TGC CCA                                    24
Thr His Thr Cys Pro Pro Cys Pro
  1               5
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..19

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
ACT CAC ACA TGC CCA CCG T GAGGATCC                                 27
Thr His Thr Cys Pro Pro
  1               5
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..34

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
ACT CAC ACA TGC TCG AGC CTT CAC GGC GGC CGC T GAGGATCC             42
Thr His Thr Cys Ser Ser Leu His Gly Gly Arg
  1               5                  10
```

Claims

1. A bispecific molecule comprising: an anti-effector cell portion and an anti-IgE portion.

2. A bispecific molecule of claim 1, wherein the anti-IgE portion is an Fc ε receptor.

3. A bispecific molecule of claim 1, wherein the anti-IgE portion is an IgE binding portion of an α chain of an Fcε receptor.

4. A bispecific molecule of claim 1, wherein the anti-effector cell portion binds an Fc receptor.

5. A bispecific molecule of claim 4, wherein the anti-effector cell portion binds an Fc receptor at a site that is not inhibited by endogenous immunoglobulin.

6. A bispecific molecule of claim 4, wherein the anti-effector cell portion binds a Fcγ receptor.

7. A bispecific molecule of claim 4, wherein the Fcγ receptor is selected from the group consisting of FcγRI, FcγRIIand FcγRIII

8. A bispecific molecule of claim 5, wherein the anti-effector cell portion binds an Fcα receptor.

9. An IgE specific effector cell comprising a bispecific molecule of claim 1, wherein the anti-effector cell portion is bound to an effector cell.

10. An IgE specific effector cell of claim 9, wherein the effector cell is an antigen presenting cell.

11. An IgE specific effector cell of claim 10, wherein the effector cell is selected from the group consisting of monocytes, macrophages, dendritic cells and natural killer cells.

12. A method for preventing an allergic reaction in a subject comprising administering to the subject an effective amount of the composition of claim 1.

13. A method for preventing an allergic reaction in a subject comprising administering to the subject an effective amount of the composition of claim 1.

14. A method for directing the immune response of a subject away from production of allergen specific IgE antibodies and towards production of allergen-specific IgG antibodies, comprising administering to the subject an effective amount of a bispecific molecule of claim 1.

Figure

h22 hinge region:

[A]

- ACT CAC ACA TGC CCA CCG TGC CCA —— CH2 — CH3
  T H T C P P C P

↓

[B]

BamHI

- ACT CAC ACA TGC CCA CCG TGA GGA TCC -
  T H T C P P *

↓

[C]

XhoI *NotI* *BamHI*

- ACT CAC ACA TGC TCG AGC CTT CAC GGC GGC CGC TGA GGA TCC
  T H T C S S L H G G R *

INTERNATIONAL SEARCH REPORT

Int 'onal Application No
PCT/US 96/09071

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K16/46 A61K35/14 A61K39/395 //C07K16/28,C07K14/735

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 05805 A (TRUSTEES OF DARTMOUTH COLLEGE) 2 May 1991 see page 5, line 6 - line 10 see claims	1,4,5, 8-14

X	EP 0 255 249 A (TRUSTEES OF DARTMOUTH COLLEGE) 3 February 1988 see page 3, line 25 - line 31 see claims	1,4-7, 9-14
Y		2,3

Y	EP 0 648 499 A (C. RA ET AL.) 19 April 1995 see examples see claims	2,3

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 1996	18. 10. 96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 96/09071

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL, vol. 57, 5 May 1989, CAMBRIDGE, MA, USA, pages 351-354, XP002014532 J-P. KINET: "Antibody-cell interactions" see page 352, right-hand column, line 7 - page 353, right-hand column, line 26 ---	2,3
A	CRITICAL REVIEWS IN IMMUNOLOGY, vol. 12, no. 3-4, 1992, BOCA RATON, FL, USA, pages 101-124, XP002014533 M. FANGER ET AL.: "Bispecific antibodies." see the whole document -----	1-14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/09071

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12 - 14 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/US 96/09071

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9105805	02-05-91	CA-A-	2067244	21-04-91
		EP-A-	0496818	05-08-92
		JP-T-	5504677	22-07-93
EP-A-255249	03-02-88	US-A-	4954617	04-09-90
		AT-T-	120802	15-04-95
		AU-B-	605771	24-01-91
		AU-A-	7527187	14-01-88
		CA-A-	1319899	06-07-93
		DE-D-	3751214	11-05-95
		DE-T-	3751214	16-11-95
		EP-A-	0629703	21-12-94
		ES-T-	2072851	01-08-95
		IL-A-	101475	31-07-94
		WO-A-	8800052	14-01-88
		JP-T-	1500195	26-01-89
EP-A-648499	19-04-95	JP-A-	7118168	09-05-95
		CA-A-	2118454	20-04-95